UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,889	05/15/2006	Ronald Aung-Din	523.1006US	3655

23280 7590 03/14/2011

Davidson, Davidson & Kappel, LLC
485 7th Avenue
14th Floor
New York, NY 10018

EXAMINER	
MCMILLIAN, KARA RENITA	
ART UNIT	PAPER NUMBER
1627	
MAIL DATE	DELIVERY MODE
03/14/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,889	AUNG-DIN, RONALD	
	Examiner	Art Unit	
	KARA R. MCMILLIAN	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38,39,44-55,57,58,60-65 and 68-74* is/are pending in the application.

4a) Of the above claim(s) *44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38,39,45-55,57,58,60-65 and 68-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12-10-10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Applicant's amendments filed December 10, 2010, amending claims 38, 45, 52, 53, 54, 58 and 60, canceling claims 40-43, 56, 59, 66-67, and adding new claims 68-74 have been entered. Claims 44, 53-55 and 60-63 were previously withdrawn. Claims 1-37 were previously canceled. Due to Applicant's amendments claims 53-55 and 60-63 which were previously withdrawn, are being rejoined as said claims now read on the elected group or species. Claims 38, 39, 45-55, 57, 58, 60-65 and 68-74 are currently presented for examination.

Response to Arguments

Due to Applicant's amendments to the claims, the previous rejection under 35 USC 112, first paragraph is hereby withdrawn. Applicant's arguments with respect to the rejection under 35 USC 112, first paragraph including the copy of the Declaration of Inventor Dr. Ronald Aung-Din, have been considered but are moot in view of the withdrawal of the rejection.

Applicant's arguments with respect to the rejection under 35 USC 103 over Franz et al. in view of Saper et al. and Aung-Din are found not persuasive.

Applicant argues that Franz is directed to topical pharmaceutical compositions wherein the active agent may be tizanidine and does not teach applying said composition at the posterior cervical area in close proximity to the brain stem. Applicant

further argues that Saper et al. describes a clinical study utilizing tizanidine tablets as a prophylactic therapy and not as an acute treatment therapy. Applicant further argues that Aung-Din teaches the treatment of migraines with a serotonin agonist and does not teach the administration of tizanidine.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, Franz teaches a topical composition comprising tizanidine to be applied to the skin for the same indications as other forms. Saper et al. teaches that oral administration of tizanidine is useful in the treatment of migraines. Therefore, it would be obvious to a person of ordinary skill in the art to use the tizanidine gel of Franz in a method of treating migraines as described in Saper et al. Aung-Din teaches the topical administration of serotonin agonists such as sumitriptan for the treatment of migraines. Thus, since both topical formulations of tizanidine and sumatriptan are useful for the treatment of migraines, one of ordinary skill in the art would be motivated to combine said ingredients with a reasonable expectation of providing an improved treatment of migraines.

In response to Applicants arguments that Saper et al. does not teach acute treatment of migraines, it would be obvious to a person of ordinary skill in the art that topical application of a gel would provide a faster onset of action as compared to oral administration since topical application involves application directly at the site of pain

whereas oral administration must first be ingested and then absorbed before relief at the site of pain. Thus it would be obvious to a person of ordinary skill in the art to treat an acute migraine with the topical formulation with a reasonable expectation that said formulation would provide a faster onset of action and provide relief from the migraine sooner than the oral formulation. Furthermore, it would be obvious to a person of ordinary skill in the art that if tizanidine can inhibit migraine formation as well as decrease severe headache intensity and decrease headache duration, as taught by Saper et al., tizanidine would be useful in the treatment of an acute migraine since administration of tizanidine during a migraine would be expected to decrease the headache intensity as well as shorten the duration of the headache.

However, even though Applicants arguments are found not persuasive the previous rejection under 35 USC 103 is hereby withdrawn as the secondary reference by Aung-Din is not applicable as prior art. Thus new rejections under 35 USC 103 are detailed below. In addition a new rejection under 35 USC 112, second paragraph, necessitated by Applicants amendments as well as a new rejection under non-statutory obviousness-type double patenting are detailed below. Accordingly, this action is made Non-final.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 38, 39, 45-52, 57, 58, 60-65 and 68-74 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2-21 of copending Application No. 12/460,966 (copending '966) in view of Saper et al. (2002, Headache, Volume 42, pages 470-482). Although the conflicting claims are not identical, they are not patentably distinct from each other because the cited claims of the instant application and the cited claims of copending '966 are substantially overlapping in scope and mutually obvious.

The recited claims of the instant application claim a method of treating migraines, cluster headaches, muscle sprains, etc. comprising applying a topical formulation comprising a unit dose of the skeletal muscle relaxant, tizanidine and further comprising a serotonin agonist such as sumatriptan, incorporated into an immediate release excipient, on to the skin at the posterior cervical area in close proximity to the brain stem wherein a therapeutic effect is within about 2 hours after topical administration.

The recited claims of copending '966 claim a method of treating migraines or cluster headaches comprising applying a topical formulation comprising an indole

serotonin agonist such as sumatriptan, incorporated into an immediate release vehicle on to the skin at the posterior cervical area in close proximity to the brain stem.

The difference between the recited claims of the instant application and the recited claims of copending '966 is that the instant application claims an additional component, tizanidine for the treatment of migraine.

Saper et al. teaches that tizanidine was shown to be superior to placebo in reducing the overall headache index, as well as mean headache days per week, severe headache days per week, average headache intensity, peak headache intensity and mean headache duration and thus supports the use of tizanidine in the treatment of chronic daily headache, including migraine, migrainous headache, and tension-type headache (abstract). Thus, Saper et al. teaches that tizanidine is useful for the treatment of migraines.

Accordingly, it is obvious to combine tizanidine to the composition claimed in copending '966 for the treatment of migraines since both tizanidine and indole serotonin agonists are known to be useful for the treatment of migraines. "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ....[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850,205 USPQ 1069, 1072 (CCPA 1980).

Thus the recited claims of the instant application and the recited claims of copending '966 are not mutually exclusive and thus not patentably distinct.

This is a provisional obviousness-type double patenting rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 57 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 57 recites the limitation "muscle relaxant" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 38, 45-52, 57, 58, 65, 68, 73 and 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Franz et al. GB 2098865 A in view of Saper et al. (2002, Headache, Volume 42, pages 470-482) and Drizen et al. U.S. Patent No. 5,897,880.

The recited claims of the instant application claim a method of treating migraines comprising applying a topical formulation comprising a unit dose of the skeletal muscle relaxant, tizanidine incorporated into an immediate release excipient on to the skin at

the posterior cervical area in close proximity to the brain stem wherein a therapeutic effect is within about 2 hours after topical administration.

Franz et al. teach topical pharmaceutical compositions, comprising a pharmacologically active agent, a water-immiscible organic solvent, an emulsifier, a co-emulsifier and water (page 2 lines 45-58). Franz et al. teach that the microemulsions of the invention may be in the form of liquids or preferably in the form of gels, which are semi-viscous, containing less water (page 3 lines 1-3). Franz et al. teach that preferable examples of active agents include especially tizanidine (page 4 lines 26-35). Franz et al. specifically disclose microemulsion composition containing tizanidine (page 4 line 65- page 5 line 17). Franz et al. further teach that in particular, they have surprisingly found that topical administration of tizanidine is feasible and accordingly teach topical pharmaceutical compositions containing tizanidine as an active agent and a method of topically administering tizanidine to a subject in need of such treatment (page 7 lines 23-28).

Franz et al. teach that in the case of tizanidine a suitable single dose is from 10 to 50 mg and this may last for up to 3 days (page 7 lines 45-46). Franz et al. teach that the microemulsions of the invention may be used for the same indication that other forms of the pharmaceutically active agents are used for, e.g. tizanidine as a myotonolytic (page 7 lines 46-49). Franz et al. disclose an example of a tizanidine microgel which contains water on page 8 lines 18-30. Claims 48-51 of Franz et al. specifically claim a topical formulation and a semi-solid pharmaceutical composition comprising tizanidine and methods of administering said composition topically.

Franz et al. do not specifically teach treatment of migraines and the hydrochloride salt of tizanidine. Franz et al. do not teach the specific dosages of tizanidine. Franz et al. do not teach applying the formulation at the posterior cervical area in close proximity to the brain stem.

Although Franz et al. do not specifically teach treatment of migraines, Franz et al. teach that the microemulsions of the invention may be used for the same indication that other forms of the pharmaceutically active agents are used for, e.g. tizanidine as a myotonolytic (page 7 lines 46-49).

Saper et al. teach that tizanidine was shown to be superior to placebo in reducing the overall headache index, as well as mean headache days per week, severe headache days per week, average headache intensity, peak headache intensity and mean headache duration and thus supports the use of tizanidine in the treatment of chronic daily headache, including migraine, migrainous headache, and tension-type headache (abstract). Saper et al. teach the hydrochloride salt of tizanidine which is the standard formulation, is commercially available as tablets for the treatment of migraines (page 471). Saper et al. further teach that administration of tizanidine is between 2 mg and 24 mg per day, with the average daily dosage being about 18 mg divided in three equal doses per day (pages 474-475).

Accordingly, it would be obvious to a person of ordinary skill in the art at the time of the instant invention to use the topical formulation of Franz et al. in the treatment of migraines since Franz et al. teach that said topical formulation can be used for the same indication as other forms of the active agent are used. Thus, since Saper et al. teach

that tizanidine in the tablet form is useful for the treatment of migraines, it would be obvious to a person of ordinary skill in the art that the topical formulation would also be useful in the treatment of migraines. Therefore based on the combination of references, an ordinary skilled artisan would be motivated to use the topical tizanidine formulation of Franz et al. for the treatment of migraines with a reasonable expectation of success. Furthermore, since tizanidine hydrochloride is a standard formulation of tizanidine and the hydrochloride salt would not be expected to alter the physical properties of the active agent, the hydrochloride salt of tizanidine is rendered obvious.

Although Franz et al. do not teach the specific dosages of the topical formulation, it is obvious to vary and/or optimize the amounts of ingredients such that the desired outcome is achieved. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980). Furthermore, it is obvious to vary and/or optimize the amount of a compound provided in the composition, in order to provide a composition having the desired properties such as the desired (ratios, concentrations, percentages, etc.). It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). In addition, since Saper et al. teaches that active concentrations of tizanidine for the treatment of migraines is between about 2 mg to about 24 mg daily with the median dosage being 18 mg per day divided in 3 equal dosages per day, it would have been obvious to a person of ordinary skill in the art to

formulate the topical tizanidine composition of Franz such that about .7 mg to about 8 mg of tizanidine is administered to the patient per unit dosage in order to achieve a total daily dosage of between about 2 mg to about 24 mg.

Although Franz et al. in view of Saper et al. does not teach applying the tizanidine composition to the posterior cervical area in close proximity to the brain stem, for the treatment of migraines, it is within the skill of an ordinary skilled artisan to determine the optimum site of application of a composition such that the desired treatment outcome is achieved.

In addition, Drizen et al. teach topical gelled compositions to be administered topically and transdermally through the skin into various sites where the drug is therapeutically effective (abstract and column 3 lines 30-35). Drizen et al. specifically teach that these formulations are specifically administered to manage pain and are applied to the skin at the sources of pain including the knees, ankles, feet and neck (column 6 lines 33-42). Drizen et al. specifically teach transdermal application of NSAIDs for conditions leading to pain (column 9 lines 4-20). Drizen et al. specifically teach in the examples in columns 13-16 that application of a topical NSAID gel to the back of the neck of patients with severe pain including severe headache pain and migraine pain was useful in the reduction of pain including the reduction of headache and migraine pain.

Accordingly, one of ordinary skill in the art at the time of the instant invention would have found it obvious to combine the teachings of Franz et al. in view of Saper et al., which renders obvious a topical composition comprising tizanidine for the treatment

of migraines, with the teachings of Drizen et al., which teach that a topical composition for the treatment of pain applied to the back of the neck which is at the posterior cervical area in close proximity to the brain stem is useful in the reduction of pain associated with migraines and headaches. Since the topical composition comprising tizanidine is rendered obvious for the treatment of migraines, an ordinary skilled artisan would be motivated to apply the composition at the posterior cervical area in close proximity to the brain stem (back of the neck) since Drizen et al. specifically teach said application is useful in the treatment of migraines and headaches.

Furthermore, since the topical composition comprising tizanidine administered at the posterior cervical area in close proximity to the brain stem (back of the neck) for the treatment of migraines is rendered obvious, it would be obvious that the composition would also provide relief within about 2 hours since administration of the same compound in essentially the same way would necessarily achieve the same results. Thus claims 51, 52 and 73 of the instant application are also rendered obvious for the same reasons and also, since the composition for the treatment of migraines is rendered obvious, the properties of the composition are also rendered obvious since a compound and its properties are inseparable. *In re Papesch,* 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

Claim 74 is also rendered obvious since Saper et al. teach the administration of tizanidine 3 times per day. It is within the skill of a person of ordinary skill in the art to optimize the amount of time between dosages of a composition such that the desired

treatment outcome is achieved. Thus in the absence of secondary considerations, such as unexpected results, claims 74 of the instant application is rendered obvious.

Therefore in view of the recited prior art references, claims 38, 45-52, 57, 58, 65, 68, 73 and 74 of the instant application are rendered obvious.

Claims 39, 60-64 and 69-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Franz et al. GB 2098865 A in view of Saper et al. (2002, Headache, Volume 42, pages 470-482) and Drizen et al. U.S. Patent No. 5,897,880 as applied to claims 38, 45-52, 57, 58, 65, 68, 73 and 74 above and further in view of Aung-Din et al. (2001, Cephalalgia, Vol. 21, pages 405-432- Provided on IDS submitted on March 10, 2010).

Claims 39, 60-64 and 69-72 of the instant application claim a method of treating migraines comprising applying a topical formulation comprising a unit dose of the skeletal muscle relaxant, tizanidine incorporated into an immediate release excipient on to the skin at the posterior cervical area in close proximity to the brain stem wherein a therapeutic effect is within about 2 hours after topical administration and further comprising a serotonin agonist such as sumatriptan.

Franz et al. in view of Saper et al. and Drizen et al. is as set forth above.

Franz et al. in view of Saper et al. and Drizen et al. does not teach the addition of sumatriptan.

Aung-Din et al. teaches a transdermal composition comprising sumatriptan for the treatment of migraines. Aung-Din specifically teaches applying 50 mg of a sumatriptan cream for the treatment of migraines.

Accordingly, at the time of the instant invention, one of ordinary skill in the art would have found it obvious to combine the teachings of Franz et al. in view of Saper et al. and Drizen et al., which renders obvious a topical composition comprising tizanidine for the treatment of migraines, with the teachings of Aung-Din et al., which teach that a topical composition comprising sumatriptan is also useful for the treatment of migraines. Thus, since both topical formulations of tizanidine and sumatriptan are useful for the treatment of migraines, one of ordinary skill in the art would be motivated to combine said ingredients with a reasonable expectation of providing an improved treatment of migraines. "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ....[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850,205 USPQ 1069, 1072 (CCPA 1980).

Thus claims 39, 60-64 and 69-72 of the instant application are rendered obvious in view of the recited prior art teachings.

Claims 53-55 and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Franz et al. GB 2098865 A in view of Saper et al. (2002, Headache, Volume 42, pages 470-482) and Drizen et al. U.S. Patent No. 5,897,880 as applied to claims 38, 45-

52, 57, 58, 65, 68, 73 and 74 above and further in view of Plachetka et al. U.S. Patent No. 6,495,535 B1.

Claims 53-55 and 64 of the instant application claim a method of treating migraines comprising applying a topical formulation comprising a unit dose of the skeletal muscle relaxant, tizanidine incorporated into an immediate release excipient on to the skin at the posterior cervical area in close proximity to the brain stem wherein a therapeutic effect is within about 2 hours after topical administration and further comprising an ergot alkaloid such as dihydroergotamine.

Franz et al. in view of Saper et al. and Drizen et al. is as set forth above.

Franz et al. in view of Saper et al. and Drizen et al. does not teach the addition of an ergot alkaloid such as dihydroergotamine.

Plachetka et al. teach formulations comprising dihydroergotamine for the treatment of migraines (see abstract). Plachetka et al. teaches that the total dosage of dihydroergotamine that will be administered to a patient per migraine attack should generally be between 0.5 mg and 5.0 mg (column 2 lines 22-29). Plachetka et al. further teaches that a single dose will usually be approximately 1 mg (column 4 lines 45-46). Plachetka et al. teaches that dihydroergotamine is dissolved in a pharmaceutically acceptable liquid and that dihydroergotamine mesylate is preferred (column 3 line 65-column 4 line 5). Plachetka et al. further teach that the dihydroergotamine composition can be administered transdermally (column 5 lines 5-6).

Accordingly, at the time of the instant invention, one of ordinary skill in the art would have found it obvious to combine the teachings of Franz et al. in view of Saper et

al. and Drizen et al., which renders obvious a topical composition comprising tizanidine for the treatment of migraines, with the teachings of Plachetka et al., which teach that dihydroergotamine is also useful for the treatment of migraines. Thus, since both tizanidine and dihydroergotamine are useful for the treatment of migraines, one of ordinary skill in the art would be motivated to combine said ingredients with a reasonable expectation of providing an improved treatment of migraines. "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ....[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850,205 USPQ 1069, 1072 (CCPA 1980).

Thus claims 53-55 and 64 of the instant application are rendered obvious in view of the recited prior art teachings.

Claims 38, 45-52, 57, 58, 65, 68, 73 and 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murdock et al. U.S. Publication No. 2002/0015713 A1 in view of Saper et al. (2002, Headache, Volume 42, pages 470-482) and Drizen et al. U.S. Patent No. 5,897,880.

The recited claims of the instant application claim a method of treating migraines comprising applying a topical formulation comprising a unit dose of the skeletal muscle relaxant, tizanidine incorporated into an immediate release excipient on to the skin at

the posterior cervical area in close proximity to the brain stem wherein a therapeutic effect is within about 2 hours after topical administration.

Murdock et al. teach methods and compositions for the relief of pain (see abstract). Murdock et al. teach a composition comprising an amine containing compound having biphasic solubility and/or an agent which enhances the activity of the amine containing compound having biphasic solubility such as a muscle relaxant for the treatment of pain (see abstract). Murdock et al. specifically teach a transdermal composition for the treatment of pain in a subject comprising a skeletal muscle relaxant in a pharmaceutically acceptable carrier suitable for transdermal delivery such as a lecithin organogel carrier [0006]. Murdock et al. further specifically teach a composition containing amine compounds having biphasic solubility such as adrenergic agonist compounds for the treatment of pain, wherein the preferred adrenergic agonist compound is tizanidine [0041].

Murdock et al. teaches that the amount of the amine containing compound having biphasic solubility useful for relieving pain transdermally typically ranges from 1 mg to about 300 mg per subject dose and may be determined by methods known in the art [0045]. Murdock et al. teach that the composition is in the form of a cream, gel, emulsion, lotion, salve, paste ointment, spray or solution and may contain carriers such as lipids including phospholipids such as lecithin, fatty oils, vasoline, etc. [0052]. Murdock et al. further teaches that the compositions are prepared by dispersing or dissolving crushed tablets, capsules or other preparations of the amine containing compounds having biphasic solubility, the muscle relaxant, and the inflammatory

compounds, which were intended for oral delivery, in a gel formed of soya lecithin and isopropyl palmitate or isopropyl myristate, alcohol, or ethoxy diglycol, or in another preferred embodiment, a pluronic gel formed of pluronic, potassium sorbate and water [0064].

Murdock et al. further teaches that the transdermal composition is applied to the skin of the subject as often as needed for the alleviation of pain, for example, applied daily, weekly, etc. to alleviate pain [0066]. Murdock et al. further teaches that the gel preparation is applied to the skin at the site or sites of pain [0067]. Claim 10 of Murdock et al. specifically claims a method for treating pain comprising the transdermal administration of a composition comprising a muscle relaxant and a pharmaceutically acceptable carrier suitable for transdermal delivery of the muscle relaxant.

Murdock et al. specifically teaches a gel formation for the treatment of pain comprising 10% of an adrenergic agonist prepared from 12 g of crushed tizanidine tablets, 6 ml of ethoxy diglycol, 26.4 ml of soya lecithin and sufficient quantity of pluronic to make the total volume of 120 ml [0158]. Thus, Murdock et al. specifically teaches a topical or transdermal gel composition comprising tizanidine for the treatment of pain.

Murdock et al. further teaches that topical application of a pain-relieving composition to the neck resulted in complete and rapid resolution of migraine like headache [0144]. Thus Murdock et al. teaches a method of treating migraine pain comprising the application of a topical pain-relieving composition to the neck of a patient.

Murdock et al. does not specifically teach treatment of migraines comprising the administration of tizanidine. Murdock et al. does not teach the hydrochloride salt of tizanidine. Murdock et al. does not teach the specific dosages of tizanidine as claimed in the instant application. Murdock et al. does not specifically teach applying the tizanidine formulation at the posterior cervical area in close proximity to the brain stem.

Although Murdock et al. does not specifically teach treatment of migraines, Murdock et al. teaches that the composition comprising tizanidine is useful for the treatment of pain, thus all pain including migraine pain is contemplated. In addition, although Murdock et al. does not teach the specific dosages of tizanidine as claimed in the instant application, Murdock et al. teaches that the compounds are generally used in amounts from 1 mg to about 300 mg per subject dose and may be determined by methods known in the art [0045].

Furthermore, Saper et al. teach that tizanidine was shown to be superior to placebo in reducing the overall headache index, as well as mean headache days per week, severe headache days per week, average headache intensity, peak headache intensity and mean headache duration and thus supports the use of tizanidine in the treatment of chronic daily headache, including migraine, migrainous headache, and tension-type headache (abstract). Saper et al. teach the hydrochloride salt of tizanidine which is the standard formulation, is commercially available as tablets for the treatment of migraines (page 471). Saper et al. further teach that administration of tizanidine is between 2 mg and 24 mg per day, with the average daily dosage being about 18 mg divided in three equal doses per day (pages 474-475).

Accordingly, it would be obvious to a person of ordinary skill in the art at the time of the instant invention to use the topical tizanidine formulation of Murdock et al. in the treatment of migraines since Murdock et al. teaches that said topical formulation can be used for the treatment of pain and Saper et al. specifically teaches that tizanidine is useful for the treatment of migraines. Therefore based on the combination of references, an ordinary skilled artisan would be motivated to use the topical tizanidine formulation of Murdock et al. for the treatment of migraines with a reasonable expectation of success. Furthermore, since tizanidine hydrochloride is a standard formulation of tizanidine and the hydrochloride salt would not be expected to alter the physical properties of the active agent, the hydrochloride salt of tizanidine is rendered obvious.

Although Franz et al. do not teach the specific dosages of the topical formulation, it is obvious to vary and/or optimize the amounts of ingredients such that the desired outcome is achieved. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980). Furthermore, it is obvious to vary and/or optimize the amount of a compound provided in the composition, in order to provide a composition having the desired properties such as the desired (ratios, concentrations, percentages, etc.). It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). In addition, since Saper et al. teaches that

active concentrations of tizanidine for the treatment of migraines is between about 2 mg to about 24 mg daily with the median dosage being 18 mg per day divided in 3 equal dosages per day, it would have been obvious to a person of ordinary skill in the art to formulate the topical tizanidine composition of Murdock et al. such that about .7 mg to about 8 mg of tizanidine is administered to the patient per unit dosage in order to achieve a total daily dosage of between about 2 mg to about 24 mg.

Although Murdock et al. in view of Saper et al. does not specifically teach applying the tizanidine composition to the posterior cervical area in close proximity to the brain stem (back of the neck), for the treatment of migraines, it is within the skill of an ordinary skilled artisan to determine the optimum site of application of a composition such that the desired treatment outcome is achieved. Furthermore, Murdock et al. teaches that topical application of a pain-relieving composition to the neck resulted in complete and rapid resolution of migraine like headache [0144]. Thus Murdock et al. teaches a method of treating migraine pain comprising the application of a topical pain-relieving composition to the neck of a patient.

In addition, Drizen et al. teach topical gelled compositions to be administered topically and transdermally through the skin into various sites where the drug is therapeutically effective (abstract and column 3 lines 30-35). Drizen et al. specifically teach that these formulations are specifically administered to manage pain and are applied to the skin at the sources of pain including the knees, ankles, feet and neck (column 6 lines 33-42). Drizen et al. specifically teach transdermal application of NSAIDs for conditions leading to pain (column 9 lines 4-20). Drizen et al. specifically

teach in the examples in columns 13-16 that application of a topical NSAID gel to the back of the neck of patients with severe pain including severe headache pain and migraine pain was useful in the reduction of pain including the reduction of headache and migraine pain.

Accordingly, one of ordinary skill in the art at the time of the instant invention would have found it obvious to combine the teachings of Murdock et al. in view of Saper et al., which renders obvious a topical composition comprising tizanidine for the treatment of migraines, with the teachings of Drizen et al., which teach that a topical composition for the treatment of pain applied to the back of the neck which is at the posterior cervical area in close proximity to the brain stem is useful in the reduction of pain associated with migraines and headaches. Since the topical composition comprising tizanidine is rendered obvious for the treatment of migraines, an ordinary skilled artisan would be motivated to apply the composition at the posterior cervical area in close proximity to the brain stem (back of the neck) since Drizen et al. specifically teach said application is useful in the treatment of migraines and headaches.

Furthermore, since the topical composition comprising tizanidine administered at the posterior cervical area in close proximity to the brain stem (back of the neck) for the treatment of migraines is rendered obvious, it would be obvious that the composition would also provide relief within about 2 hours since administration of the same compound in essentially the same way would necessarily achieve the same results. Thus claims 51, 52 and 73 of the instant application are also rendered obvious for the same reasons and also, since the composition for the treatment of migraines is

rendered obvious, the properties of the composition are also rendered obvious since a compound and its properties are inseparable. *In re Papesch,* 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

Claim 74 is also rendered obvious since Murdock et al. teaches that the composition should be applied to the skin as often as need for the alleviation of pain. It is within the skill of a person of ordinary skill in the art to optimize the amount of time between dosages of a composition such that the desired treatment outcome is achieved. Thus in the absence of secondary considerations, such as unexpected results, claims 74 of the instant application is rendered obvious.

Therefore in view of the recited prior art references, claims 38, 45-52, 57, 58, 65, 68, 73 and 74 of the instant application are rendered obvious.

Claims 39, 60-64 and 69-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murdock et al. U.S. Publication No. 2002/0015713 A1 in view of Saper et al. (2002, Headache, Volume 42, pages 470-482) and Drizen et al. U.S. Patent No. 5,897,880 as applied to claims 38, 45-52, 57, 58, 65, 68, 73 and 74 above and further in view of Aung-Din et al. (2001, Cephalalgia, Vol. 21, pages 405-432- Provided on IDS submitted on March 10, 2010).

Claims 39, 60-64 and 69-72 of the instant application claim a method of treating migraines comprising applying a topical formulation comprising a unit dose of the skeletal muscle relaxant, tizanidine incorporated into an immediate release excipient on to the skin at the posterior cervical area in close proximity to the brain stem wherein a

therapeutic effect is within about 2 hours after topical administration and further comprising a serotonin agonist such as sumatriptan.

Murdock et al. in view of Saper et al. and Drizen et al. is as set forth above.

Murdock et al. in view of Saper et al. and Drizen et al. does not teach the addition of sumatriptan.

Aung-Din et al. teaches a transdermal composition comprising sumatriptan for the treatment of migraines. Aung-Din specifically teaches applying 50 mg of a sumatriptan cream for the treatment of migraines.

Accordingly, at the time of the instant invention, one of ordinary skill in the art would have found it obvious to combine the teachings of Murdock et al. in view of Saper et al. and Drizen et al., which renders obvious a topical composition comprising tizanidine for the treatment of migraines, with the teachings of Aung-Din et al., which teach that a topical composition comprising sumatriptan is also useful for the treatment of migraines. Thus, since both topical formulations of tizanidine and sumatriptan are useful for the treatment of migraines, one of ordinary skill in the art would be motivated to combine said ingredients with a reasonable expectation of providing an improved treatment of migraines. "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ....[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850,205 USPQ 1069, 1072 (CCPA 1980).

Thus claims 39, 60-64 and 69-72 of the instant application are rendered obvious in view of the recited prior art teachings.

Claims 53-55 and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murdock et al. U.S. Publication No. 2002/0015713 A1 in view of Saper et al. (2002, Headache, Volume 42, pages 470-482) and Drizen et al. U.S. Patent No. 5,897,880 as applied to claims 38, 45-52, 57, 58, 65, 68, 73 and 74 above and further in view of Plachetka et al. U.S. Patent No. 6,495,535 B1.

Claims 53-55 and 64 of the instant application claim a method of treating migraines comprising applying a topical formulation comprising a unit dose of the skeletal muscle relaxant, tizanidine incorporated into an immediate release excipient on to the skin at the posterior cervical area in close proximity to the brain stem wherein a therapeutic effect is within about 2 hours after topical administration and further comprising an ergot alkaloid such as dihydroergotamine.

Murdock et al. in view of Saper et al. and Drizen et al. is as set forth above.

Murdock et al. in view of Saper et al. and Drizen et al. does not teach the addition of an ergot alkaloid such as dihydroergotamine.

Plachetka et al. teach formulations comprising dihydroergotamine for the treatment of migraines (see abstract). Plachetka et al. teaches that the total dosage of dihydroergotamine that will be administered to a patient per migraine attack should generally be between 0.5 mg and 5.0 mg (column 2 lines 22-29). Plachetka et al. further teaches that a single dose will usually be approximately 1 mg (column 4 lines 45-

46). Plachetka et al. teaches that dihydroergotamine is dissolved in a pharmaceutically acceptable liquid and that dihydroergotamine mesylate is preferred (column 3 line 65-column 4 line 5). Plachetka et al. further teach that the dihydroergotamine composition can be administered transdermally (column 5 lines 5-6).

Accordingly, at the time of the instant invention, one of ordinary skill in the art would have found it obvious to combine the teachings of Murdock et al. in view of Saper et al. and Drizen et al., which renders obvious a topical composition comprising tizanidine for the treatment of migraines, with the teachings of Plachetka et al., which teach that dihydroergotamine is also useful for the treatment of migraines. Thus, since both tizanidine and dihydroergotamine are useful for the treatment of migraines, one of ordinary skill in the art would be motivated to combine said ingredients with a reasonable expectation of providing an improved treatment of migraines. "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ....[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850,205 USPQ 1069, 1072 (CCPA 1980).

Thus claims 53-55 and 64 of the instant application are rendered obvious in view of the recited prior art teachings.

Conclusions

Claims 38, 39, 45-55, 57, 58, 60-65 and 68-74 are rejected. Claim 44 is withdrawn. Claims 1-37, 40-43, 56, 59 and 66-67 are canceled. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KARA R. MCMILLIAN whose telephone number is (571)270-5236. The examiner can normally be reached on Monday- Friday from 9:30 am- 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kara R. McMillian/
Examiner, Art Unit 1627

KRM

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627